FDA Experience with Post-Licensure Data Collection

Biological Therapeutics for Rare Plasma Protein Disorders
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Definition

- *Postmarketing study commitments: Studies required of or agreed to by a sponsor that are conducted after FDA has approved a product for marketing.*

Purpose of PMC Studies

- *FDA uses postmarketing study commitments to gather additional information about a product's safety, efficacy, or optimal use.*

Timing of PMCs

- *Agreements with sponsors to conduct postmarketing studies can be reached either before or after FDA has granted approval to a sponsor to market a product.*

Authority for Monitoring/Reporting PMC Progress

- *The Food and Drug Administration Modernization Act of 1997 (FDAMA) amended the Food, Drug and Cosmetic Act by adding a new section 506B (21 U.S.C. 356b). This section provides additional authority for monitoring the progress of postmarketing studies that drug and biologic applicants have agreed to conduct.*

Why Monitor PMCs?

- *Congress enacted this section in response to concerns expressed by the Food and Drug Administration and the public about the timeliness of completing postmarketing studies and about the need to update drug labeling with information obtained from such studies. A May ’96 OIG Report highlighted concerns.*

Reporting Requirements for Sponsor *and* FDA

- *The new provision requires sponsors of approved drugs and biologics to report to FDA annually on the progress of their postmarketing study commitments.*
- *In addition, FDA must publish annually in the Federal Register a report that provides information on the status of postmarketing studies that sponsors have agreed to conduct and for which annual reports have been submitted.*

Reporting Requirements for Sponsor *and* FDA (cont.)

- *FDA also agreed to make basic information about the status of each postmarketing study commitment available to the public on the Internet.*
- *The **postmarketing study information** includes the basic information the FDA committed to make available to the public.*

- *The information (excluding proprietary information) currently available to search includes:*
  - *commitments made with the Center for Biologics Evaluation and Research (CBER) at any time, and*
  - *commitments made with the Center for Drug Evaluation and Research (CDER) since January 1, 1991.*
- *Only commitments that have been reviewed for accuracy are included in the current list. The information will be updated quarterly (in April, July, October, and January).*

Online FDA PMC Database

- *New commitments, commitments not previously listed that have been reviewed for accuracy, and status updates for existing commitments will be added to the list with the updates.*
- *Questions or comments may be sent to the Postmarketing Study Commitment Coordinator at pmcweb@cder.fda.gov*

PMC FDA Website

- *For CDER and CBER PMC study status:*

  http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

PMC Guidance for Industry

- *Published draft guidance:*
  - ***Guidance for Industry***
  - ***Reports on the Status of Postmarketing Studies - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997***
- *http://www.fda.gov/cber/gdlns/post040401.htm*

Stastistics re PMCs Online

- *Report to Congress re: PMCs:*
- *http://www.fda.gov/cber/fdama/pstmrktfdama130.htm*

Problems with Sponsor Timeliness with Initiating/Completing PMC Studies?

- *Various factors may delay initiation, progress, and completion of PMC studies.*
- *As of February 2002:*
  - *44 of 301 PMC Commitments for Biologics had been completed.*
  - *882 of 2400 PMC Commitments for Drugs had been completed.*

Problems with PMC Timeliness

- *A recent Reuters news release claimed, citing FDA data, that 46 percent of 91 studies started since 1992 of drugs that received accelerated approval are incomplete.*
- *“Companies have been selling these products to the public for an average of one year and 10 months and up to six years and nine months without … initiating the required studies," according to the report.*

Problems with Timeliness of PMCs (source: Reuters)

- *"In 2003, it [FDA] published figures showing 349 studies for chemical-based drugs were completed, while 61 percent of the 1,339 outstanding studies had not been started."*
- *An informal June '05 analysis from the FDA website data showed 20% of 66 CBER PMCs fulfilled/released, 12% submitted, 8% delayed, 21% not initiated, and 39% ongoing.*
- *Will improvements in FDA's tracking system for PMCs help assure more timely completion and reporting of PMC study results?*

FDA currently has authority to take legal action against applicants who fail to complete postmarketing studies performed under accelerated approval provisions [21 CFR 314, subpart H and 601 subpart E] and deferred pediatric studies.

- *Failure to complete studies under accelerated approval may result in a withdrawal of approval [withdrawing the drug from the market] or modification to labeling claims.*
- *Failure to complete deferred pediatric studies and to submit pediatric labeling may cause the product to be misbranded. FDA may initiate seizure or injunction actions.*

Other Problems with PMCs

- *Good Clinical Practice Deficiencies led to rejection of a PMC study by the EMEA.*
- *Lack of blinding in a RCT led to grossly unequal dropouts in the treated/untreated patient groups, invalidating the study conclusion that the test product was harmful.*

Lessons Learned from PMCs

- *PMC studies can provide valuable additional data regarding efficacy and safety of products receiving either "regular" or accelerated approval.*
- *PMC studies can help to further validate surrogate endpoints*
- *There would appear to be room for improvement in the timeliness of PMC study initiation/completion in many instances.*